A process for preparing remifentanil by conversion of the nitrile group of a cyanopiperidinyl propionate derivative to an ester group. Advantageously, with this process the number of steps for preparing remifentanil from commercial products is significantly reduced, compared to the processes known in the art.
The present invention relates to a process for preparing remifentanil, intermediates thereof, use of said intermediates and processes for the preparation thereof.

BACKGROUND ART

The 4-anilidopiperidine class of opioid analgesics is widely used during surgical procedures as adjuncts to anesthesia. Since the prototype, fentanyl, 1, was introduced in the 1960s, several other derivatives (sufentanil, 2, alfentanil, 3) have been developed in order to improve its properties. Among them is of special interest remifentanil, because of its ultrashort duration of action. This feature makes it particularly suitable for anesthesia, since provides a more rapid recovery and no accumulation of drug during continuous infusion.

Remifentanil is the INN name of the chemical compound 4-(methoxycarbonyl)-4-[(1-oxopropyl)phenylamino]-1-piperidine propanoic acid methyl ester. It has the following chemical formula:

\[
\text{MeOOC} \quad \text{N} \quad \text{Ph} \\
\text{COOMe}
\]

It is currently marketed under the trademark ULTIVA, as its hydrochloride salt form.

Remifentanil was disclosed in the EP383579A patent application. Despite the interesting properties of this compound, few processes for its preparation have been described.
EP383579A discloses generically two processes that may lead to remifentanil: by reaction of a piperidine derivative with a reagent serving to introduce the substituent of the N in the piperidine ring, and by esterifying the carboxy group of the substituent of the N in the piperidine ring. In particular, example 10 of said application describes a process for preparing remifentanil by reaction of the corresponding piperidine with methyl acrylate to render remifentanil as an oil. The hydrochloride salt is prepared by dissolving the free base in methanol and addition of hydrogen chloride (Scheme 1).

An optimized synthesis for the preparation of said piperidine intermediate is described in Kiricovici V. D. et al. J. Serb. Chem. Soc. 67(12):793-802 (2002). It starts from 1-benzyl-4-piperidone and comprises seven steps with an 22% overall yield.

International application WO0140184A2 relates to (phenylamino)-4-piperidineanilides as intermediates for the preparation of derivatives and analogs of fentanyl (Scheme 2). It also mentions in example 10B the steps of a possible route of synthesis for preparing remifentanil, using said intermediates, by alkylation of 4-(phenylamino)-4-piperidinecarboxyl-N-methylanilide with methyl acrylate, conversion of the tertiary amide to methyl ester and reaction with propionyl chloride. It should be noticed that in this approach the starting material is quite far from commercial available precursors.
SUMMARY OF THE INVENTION

[0009] The problem to be solved by the present invention is to provide an alternative process for preparing remifentanil. The process is advantageous in several aspects over the processes of the prior art.

[0010] Accordingly, a first aspect of the invention relates to a process for preparing a compound of formula (I) or pharmaceutically acceptable salts thereof

\[
\text{(I)}
\]

wherein \(R_1^1\) and \(R_2^2\) are independently a \(C_1-C_4\) linear or branched alkyl or H, which comprises converting the nitrile group of a compound of formula (II)

\[
\text{(II)}
\]

wherein \(R_3\) is a \(C_1-C_4\) linear or branched alkyl or H, into a \(-COOR_3\) group, wherein \(R_1^1\) is as defined above, in an appropriate solvent system, and optionally, when in the resulting compound of formula (I) at least one of \(R_1^1\) and \(R_2^2\) are not a methyl group transforming said R to a methyl group, and optionally, if desired, further converting the compound of formula (I) or a salt thereof into a pharmaceutically acceptable salt thereof.

[0011] A second aspect of the invention relates to a compound of formula (II):

\[
\text{(II)}
\]

wherein \(R_3\) is as defined above.

[0012] A third aspect of the invention relates to a compound of formula (III):

\[
\text{(III)}
\]

wherein \(R_3\) is as defined above.

[0013] A fourth aspect of the invention relates to the use of a compound of formula (II) as defined in the second aspect of the invention and its corresponding embodiments, for the preparation of remifentanil.

[0014] A fifth aspect of the invention relates to the use of a compound of formula (III) as defined in the third aspect of the invention and its corresponding embodiments, for the preparation of remifentanil.

[0015] A sixth aspect of the invention relates to a process for preparing a compound of formula (II) as defined in the second aspect of the invention and its corresponding embodiments, which comprises the acylation of a compound of formula (III)

\[
\text{(III)}
\]

wherein \(R_3\) is as defined above, with an acylating agent able to introduce a propionyl group.

[0016] A seventh aspect of the invention relates to a process for preparing a compound of formula (III) as defined in the third aspect of the invention and its corresponding embodiments, which comprises the reaction of 3-(4-oxo-1-piperidine)propanoic acid, \(C_1-C_4\) alkyl ester with aniline and a source of cyanide, under Streeker type reaction conditions.

[0017] The process of the present invention presents several advantages that are highly desirable for the manufacture of remifentanil on an industrial scale. It provides an alternative process, wherein the number of steps for preparing remifentanil from commercial products is significantly reduced compared to the processes known in the art, the starting products are readily available, the process is economically advantageous and renders remifentanil in a highly simplified and efficient manner.
Prior numerous attempts described in the literature failed to reduce the number of steps of remifentanil synthesis (e.g. by unsuccessfully trying the direct conversion of an anilino-nitrile intermediate to an anilino-ester intermediate) (Kirkoejevic V. D. et al. J. Serb. Chem. Soc. 67(12):793-802 (2002)). One embodiment of the invention not only reduces the number of steps of the synthesis route but also succeeds in the direct conversion of the nitrile group to the ester group. Thus, remifentanil and even its hydrochloride salt may be obtained in one step from the nitrile intermediate, which may be easily obtained from simple and cheap starting materials.

The intermediates provided by the present invention allow the preparation of remifentanil in very few steps compared to the processes known in the art.

DEFINITIONS

By C₃₋C₄ alkyl or C₁₋C₄ linear or branched alkyl as used herein, it is understood a linear or branched alkyl group which contains up to 4 carbon atoms. Thus it includes a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl group.

By C₂₋C₄ linear or branched alkyl as used herein, it is understood a linear or branched alkyl group which contains from 2 to 4 carbon atoms. Thus it includes a ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl group.

DETAILED DESCRIPTION OF PARTICULAR EMBODIMENTS

As said above, in the process according to the first aspect of the invention the nitrile group of a compound of formula (II) is converted into a —COOR¹ group, wherein R¹ is a C₁₋C₄ linear or branched alkyl or H.

The best conditions to carry out the process vary according to the parameters considered by the person skilled in the art, such as the R groups, the solvents, temperature and similar. Such reaction conditions may be easily determined by the person skilled in the art by routine tests, and with the teaching of the examples included in this document.

The nitrile group may be converted to a —COOH group by hydrolysis in an acid or basic medium. Suitable acidic conditions include strong acids such as hydrochloric acid, sulphuric acid or trifluoroacetic acid in polar solvents such as water or acetic acid. Suitable basic conditions include sodium or potassium hydroxide as bases and water or alcohols as solvents. Bacteria can also be used for this transformation. Typical details of this process embodiment can be found in Laroc, R. C. Comprehensive Organic Transformation, 2nd Ed, Wiley-VCH, p. 1986. The nitrile group may be converted to a —COOR¹ group wherein R¹ means C₁₋C₄ linear or branched alkyl by an alcoholysis reaction. Typical details of this process embodiment can be found in Laroc, R. C. Comprehensive Organic Transformation, 2nd Ed, Wiley-VCH, p. 1987.

As said in the first aspect of the invention, when in the compound resulting from the conversion of the nitrile group to a COOR¹ group at least one of R² and R⁴ are not a methyl group, the conversion is optionally followed by a transformation of said R to a methyl group. Said transformation of said R may be effected by an esterification reaction, when said R is H, or by a transesterification reaction when said R is a C₂₋C₄ linear or branched alkyl. Said esterification reaction may be carried out with a hydrogen chloride solution in methanol e.g. as described in Synth. Commun. 1998, 28, 471-474. Said transesterification reaction may also be carried out with a hydrogen chloride solution in methanol e.g. as described in Synth. Commun. 1998, 28, 471-474.

In a preferred embodiment, the nitrile group is converted to a —COOR¹ group, wherein R¹ means a C₁₋C₄ linear or branched alkyl by an alcoholysis reaction. Therefore, the solvent system for carrying out said conversion preferably comprises a C₁₋C₄ linear or branched alcohol and an organic or inorganic strong acid. The strong acid is preferably selected from the group consisting of hydrochloric acid, hydrobromic acid, methanesulphonic acid and sulphuric acid.

The alcoholysis reaction is preferably carried out at a temperature comprised in the range from 80°C to 0°C. More preferably from 40°C to 10°C, and yet more preferably at room temperature.

Preferably the alcoholysis is a methanalysis or an ethanalysis. Therefore, the alcohol is preferably selected from the group consisting of methanol and ethanol, more preferably methanol. When methanol is employed, the nitrile is directly converted to a COOMe group. When ethanol is employed the nitrile group is converted to a COOEt group.

In one embodiment, the process comprises the conversion of the nitrile group of a compound of formula (II) wherein R³ is an ethyl group, into a COOEt group in methanol and in the presence of a strong organic or inorganic acid and the ethyl ester group(s) of the compound obtained are further transformed to methyl ester by transesterification reaction in methanol.

In a preferred embodiment, R¹, R² and R⁴ are a methyl group. In a particularly preferred embodiment, R¹, R² and R⁴ are a methyl group, the alcoholysis reaction is a methanalysis and is carried out in methanol and in the presence of an organic or inorganic strong acid. In a yet more particularly preferred embodiment, the strong acid is hydrochloric acid, advantageously in this case, because remifentanil hydrochloride salt is directly obtained.

The remifentanil hydrochloride salt thus obtained may be further purified if necessary, by recrystallization. Alternatively, it may be purified by conversion of the salt to the free base and again conversion to the desired pharmaceutical salt.

Compounds of formula (I) obtained by the process of the present invention may be converted into pharmaceutically acceptable salts, and salts may be converted into free compounds, by conventional methods.

Generally, the meaning of R² in the compound of formula (I) obtained will be the same as the meaning of R² in the intermediate of formula (II) employed. However, in some cases it may be different, since, as would be well-known to the skilled in the art, depending on the reaction conditions employed for the transformation of the nitrile group of the intermediate of formula (II), the group COOR² may suffer a transesterification reaction (e.g. when the conversion of the nitrile group is done by means of an alcoholysis and the alcohol employed is R²—OH, wherein R² is different from R¹ and in the compound of formula (I) R¹=R³) or a hydrolysis reaction (e.g. when the conversion of the nitrile group is done by means of a hydrolysis reaction and R² does not mean H). In a preferred embodiment, R² in the compound of formula (I) obtained has the same meaning as R¹ in the intermediate of formula (II) employed.
Preferably, the intermediate of formula (II) is prepared by acylation of a compound of formula (III) with an acylating agent able to introduce a propionyl group.

Preferably R is methyl.

Suitable acylating agents include propionyl halides, such as propionyl chloride, propionyl bromide, anhydrides such as propionic anhydride, including also mixed or fluorated anhydrides containing a propionyl moiety. Preferably, the acylating agent is selected from the group consisting of propionyl chloride, propionyl bromide and propionic anhydride. More preferably, the acylating agent is propionyl chloride.

The acylation reaction for preparing the compound of formula (II) may be carried out in a variety of solvents. Preferably, when an acylating agent is not an acy়oxide, the solvent is a polar aprotic solvent. More preferably, the solvent is selected from the group consisting of dichloromethane, tetrahydrofuran, dimethoxyethane and toluene. Particularly good results are obtained when it is carried out in toluene. When the acylating reagent is an anhydride, propionic acid can be used also as solvent. The reaction can be carried out in the presence of an acylation catalyst, such as dimethylaminopyridine. The reaction is preferably carried out at a temperature comprised in the range from room temperature to 100°C. More preferably from 45°C to 90°C, and yet more preferably at 85°C.

Preferably, the intermediate of formula (III) is prepared by condensation of 3-(4-oxo-1-piperidine)propanoic acid, C1-C4 alkyl ester with aniline and an a source of cyanide, under Strecker type reaction conditions. Suitable source of cyanide include organic and inorganic cyanides, such as ammonium cyanide, trimethylsilyl cyanide, sodium cyanide, and potassium cyanide. Preferably, the source of cyanide is sodium cyanide.

The condensation reaction with aniline to render the compound of formula (III) may be carried out in a variety of solvents. Suitable solvents are alcohols, acetic acid and chlorinated solvents, preferably selected from the group consisting of C1-C4 linear or branched alcohols, such as methanol, ethanol, 2-propanol, 1-propanol, and dichloromethane. Preferably, it is carried out in methanol, in order to avoid transesterification by-products.

The condensation reaction with aniline is preferably carried out in the presence of an acid catalyst, such as acetic acid, trifluoroacetic acid, aqueous hydrochloric acid, p-toluenesulfonic acid or methanesulfonic acid. More preferably, the acid catalyst is acetic acid. Particularly good results were obtained employing methanol as a solvent and acetic acid as catalyst.

The reaction may be carried out at a temperature range from 0°C to 40°C, preferably at room temperature. In a preferred embodiment the temperature is subsequently increased to a temperature comprised in the range from 40°C to 70°C.

The 3-(4-oxo-1-piperidine)propanoic acid, C1-C4 alkyl ester may be prepared in different ways, preferably by way of a conjugated addition reaction between 4-piperidone and the corresponding C1-C4 alkyl acrylate. The methyl or ethyl ester are preferred, most preferred is the methyl ester. The reaction may be carried out in an inert organic solvent, such as acetonitrile, a C1-C4 linear or branched alcohol, e.g. methanol or ethanol, an ether e.g. diethyl ether, dioxane, and an aromatic hydrocarbon, e.g. benzene, toluene and more preferably in methanol.

Preferred compounds of formula (II) are those wherein R2 is methyl or ethyl. Yet more preferred compounds of formula (II) are those wherein R2 is methyl.

Preferred compounds of formula (III) are those wherein R2 is methyl or ethyl. Yet more preferred compounds of formula (III) are those wherein R2 is methyl.

Throughout the description and claims the word “comprise” and variations of the word, such as “comprising”, is not intended to exclude other technical features, additives, components, or steps.

Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples are provided by way of illustration, and is not intended to be limiting of the present invention.

EXAMPLES

Example 1
3-(4-oxo-1-piperidine)propanoic Acid, Methyl Ester

To a suspension of 4-piperidone hydrate hydrochloride (125 g, 0.81 mol) and methyl acrylate (96 ml, 1.07 mol) in methanol (800 ml) is added potassium carbonate (169 g, 1.22 mol) at room temperature. The suspension is stirred at room temperature for 4 hours. The suspension is then filtered and the filtrate concentrated to a residue. The residue is dissolved in water (170 ml) and extracted with ethyl acetate (1 L). The layers are separated and the aqueous layer is extracted again with ethyl acetate (2×250 ml). The combined organic phases are dried over anhydrous sodium sulphate and concentrated to give 3-(4-oxo-1-piperidine)propanoic acid, methyl ester (133.3 g, 88%) as an oil that solidifies on standing.
Example 2
3-(4-cyano-4-phenylamino-1-piperidine)propanoic Acid, Methyl Ester

To a stirred mixture of 3-(4-oxo-1-piperidine)propanoic acid, methyl ester (180 g, 0.97 mol), aniline (143 ml, 1.57 mol) and acetic acid (145 ml, 2.54 mol) in methanol (900 ml) is added dropwise a solution of sodium cyanide (50 g, 1.02 mol) in water (160 ml) at room temperature for a period of 30 minutes. The mixture is then stirred at 60°C for four hours. Then the mixture is cooled to 0°C and basified to pH 10-11 with sodium hydroxide 33% while a white precipitate is formed. 350 ml of water are added and the mixture is allowed to stir at 0°C overnight.

The mixture is then filtered with suction and the solid washed with a mixture 1:1 of water and methanol to yield 3-(4-phenylamino-4-cyan-1-piperidine)propanoic acid methyl ester (124.8 g, 45%) as a white solid; m.p. 96-100°C.

1H-NMR (250 MHz, CDCl₃): δ 7.24 (t, 2H), 6.91 (m, 3H), 3.68 (s, 3H), 2.88-2.70 (m, 2H), 2.74 (t, 2H), 2.49 (t, 2H), 2.54-2.40 (m, 2H), 2.32 (d, 2H), 1.89 (ddd, 2H). 13C-NMR (62.5 MHz, CDCl₃): δ 172.5, 143.0, 129.0, 120.7, 120.3, 117.6, 52.9, 52.7, 51.4, 48.8, 35.8, 32.1.

Example 3
3-[4-cyano-4-{(1-oxopropyl)phenylamino}-1-piperidine]propanoic Acid, Methyl Ester

Propionyl chloride (9.5 ml, 108.73 mmol) is added to a stirred solution of 3-[4-phenylamino-4-cyan-1-piperidine]propanoic acid methyl ester (10 g, 34.80 mmol) in toluene (100 ml). The mixture is refluxed for 3 hours, then triethylamine (5 ml, 35.92 mmol) is added gradually over 1 h and the stirring continued overnight. The mixture is cooled to room temperature and the contents are poured into a 25% potassium carbonate solution (100 ml).

The layers are separated and the aqueous layer is extracted with toluene (2x60 ml). The combined organic layers are dried over magnesium sulphate, filtered and concentrated under vacuum to yield 3-[4-cyano-4-{(1-oxopropyl)phenylamino}-1-piperidine]propanoic acid, methyl ester (11.9 g, 99%) as an oil, which is used in the next reaction without further purification.

1H-NMR (250 MHz, CDCl₃): δ 7.46-7.38 (m, 3H), 7.20-7.11 (m, 2H), 3.63 (s, 3H), 2.83 (d, J=12.6 Hz, 2H), 2.67 (t, J=7.24 Hz, 2H), 2.42 (t, J=7.24 Hz, 2H), 2.50-2.28 (m, 4H), 1.91 (q, J=7.34 Hz, 2H), 1.54 (2t, J=12.47 Hz, 2H), 0.94 (t, J=7.3 Hz, 3H). 13C-NMR (62.5 MHz, CDCl₃): δ 174.2, 172.6, 138.3, 130.3, 129.7, 129.3, 129.7, 120.7, 120.3, 117.6, 52.9, 52.7, 51.4, 48.8, 35.8, 32.1, 29.5, 8.9.

Example 4
3-[4-methoxycarbonyl-4-{(1-oxopropyl)phenylamino}-1-piperidine]propanoic Acid, Methyl Ester, Hydrochloride

HCl → MeOH
What is claimed is:

1. A process for preparing a compound of formula (I) or pharmaceutically acceptable salts thereof

\[
{(I)} \quad \text{(II)}
\]

wherein each of \( R^1 \) and \( R^2 \) are independently a \( C_1-C_4 \) linear or branched alkyl or \( H \); the process comprising: converting the nitrile group of a compound of formula (II)

Example 5

3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, Methyl Ester

[0058] 3-[4-cyano-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester (10.5 g. 30.66 mmol) is dissolved in a 3.4 M solution of hydrogen chloride in methanol (72 ml) and the solution stirred at room temperature for 24 hours while a white precipitate is formed. The mixture is then cooled to 0°C. and the stirring continued for 3 hours. The mixture is filtered to yield 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester hydrochloride (7.8 g, 62%) as a white solid.

[0059] The hydrochloride salt is recrystallised heating with methyl ethyl ketone and adding methanol while heating until the solid goes back into solution. Upon cooling the salt precipitates as a white solid.
6. The process according to claim 1, further comprising the step of preparing the compound of formula (II) by acylation of a compound of formula (III)

\[
\text{NC} \quad \text{H} \quad \text{Ph}
\]

wherein \( R^3 \) is a \( C_1-C_4 \) linear or branched alkyl or H, with an acylating agent able to introduce a propionyl group.

7. The process according to claim 6, further comprising the step of preparing the compound of formula (III) by reaction of 3-(4-oxo-1-piperidine)propanoic acid, \( C_1-C_4 \) alkyl ester with aniline and a source of cyanide, under Strecker type reaction conditions.

8. A compound of formula (II):

\[
\text{NC} \quad \text{N} \quad \text{N} \quad \text{Ph}
\]

wherein \( R^3 \) is a \( C_1-C_4 \) linear or branched alkyl or H.

9. A compound according to claim 8, wherein \( R^3 \) is methyl or ethyl.

10. A compound according to claim 9, wherein \( R^3 \) is methyl.

11. A compound of formula (III):

\[
\text{NC} \quad \text{H} \quad \text{Ph}
\]

wherein \( R^3 \) is a \( C_1-C_4 \) linear or branched alkyl or H.

12. A compound according to claim 11, wherein \( R^3 \) is methyl or ethyl.

13. A compound according to claim 12, wherein \( R^3 \) is methyl.

14. A method for the preparation of remifentanil using a compound of formula (II) as defined in claim 8; the method comprising chemically converting at least a portion of the compound of formula (II).

15. A method for the preparation of remifentanil using a compound of formula (III) as defined in claim 11; the method comprising chemically converting at least a portion of the compound of formula (III).

16. A process for preparing a compound of formula (II) as defined in claim 8, which comprises acylating a compound of formula (III)

\[
\text{COOR}^2
\]

wherein \( R^3 \) is a \( C_1-C_4 \) linear or branched alkyl or H, with an acylating agent able to introduce a propionyl group.

17. A process for preparing a compound of formula (III) as defined in claim 11, which comprises reacting 3-(4-oxo-1-piperidine)propanoic acid, \( C_1-C_4 \) alkyl ester with aniline and a source of cyanide, under Strecker type reaction conditions.

18. The process according to claim 6, wherein each of \( R^1 \), \( R^2 \) and \( R^3 \) is a methyl group, and said solvent system comprises methanol and hydrochloric acid.

19. The process according to claim 16, wherein \( R^3 \) is methyl.

20. The process according to claim 17, wherein \( R^3 \) is methyl.

* * * * *